THE INVENTION

The present invention is directed to a sustained-release pharmaceutical composition containing an ionic prostanoic acid derivative, and an ionic compound having an opposite charge to that of the ionic prostanoic acid derivative. The ionic compound is capable of enhancing the hydrophobic property of the ionic prostanoic acid derivative. Unexpectedly, these ionic complexes exhibit an excellent sustained release effect.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner rejected claims 1-16 under 35 U.S.C. § 112, first paragraph, as allegedly being nonenabled for the full scope of the claims. The Examiner suggests limiting prostanoic acid derivatives to prostaglandin I_2 derivatives. In response, Applicants respectfully traverse the rejection.

Applicants respectfully point out that the proper standard for determining whether the claims are adequately enabled is whether undue experimentation is required by one skilled in the art to practice the invention. The analysis includes consideration of factors such as the amount of guidance provided in the application and the presence of working examples. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1985); *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

In the instant case, the claims are adequately enabled as one of ordinary skill in the art can practice the claimed invention without undue experimentation. As set out in *Wands*, "a *considerable* amount of experimentation is permissible, if it is merely *routine*, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should precede." *In re Wands*, 8 USPQ2d at 1404 (quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982) (Emphasis added).

Clearly, in the instant application, the amount of experimentation is not undue as the specification gives adequate guidance and 41 working examples. For example, when the ionic prostanoic acid derivative is anionic, a cationic compound such

as those having an ammonium group, a pyridinium group, a phosphonium group, or a sulfonium group in the molecule is used. (The Examiner's attention is respectfully directed to page 14, line 7, bridging to page 15, line 21 of the present specification). If, on the other hand, the ionic prostanoic acid derivative is cationic, an anionic compound such as those having a carboxyl group, a sulfate group, a sulfonate group, or a phosphate group in the molecule is used. (Please see, page 15, line 22, bridging to page 16, line 19 of the present specification).

In addition, many examples are set forth in the specification. For instance, examples 1-17 teach various gel preparations. Moreover, examples 18-19 teach liquid preparations. Examples 19 and 20-24 teach emulsions. Examples 26-30 teach various oily preparations. Examples 31-34 teach further gel examples and examples 35-38 teach cream formulations. Other suitable formulations are set forth in examples 39-41.

Based on the evidence regarding the detailed guidance set forth above, the specification at the time the application was filed, would have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

Moreover, Applicants assert that the number of working examples disclosed in the specification is sufficient to enable the full scope of the claims. Applicants are not required to disclose every species of a genus. For example, in *In re Angstadt*, the court decided that Applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art" and that "the disclosure of forty working examples sufficiently described the subject matter of claims directed to a generic process." 537 F.2d at 502-03, 190 USPQ at 218.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner has rejected claims 1-16 under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner alleges that the term "prostanoic acid

derivative" is a relative term which renders the claim indefinite. In response, Applicants respectfully traverse the rejection.

The Examiner attention is respectfully directed to page 8, line 20, of the specification wherein various ionic prostaglandin derivatives are set forth. As set forth therein, ionic prostanoic acid derivatives refer to ionic prostaglandins A_2, B_2, C_2, D_2, E_2, $F_{2\alpha}$, G_2, H_2, I_2, and J_2 and these derivatives can be used without any particular restriction. Moreover, on page 14, lines 2-4, the term "ionic" is set forth as being a compound containing one or more charged groups in the molecule thereof. Clearly, with these definitions, a skilled person would be appraised of the term "ionic prostaglandin derivative" and understand its meaning. As such, the metes and bounds of the claim are well defined. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

FIRST REJECTION UNDER 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-13, and 16 under 35 U.S.C. § 103(a) as allegedly being obvious over JP 02262519 ("JP '519"). The Examiner states that JP '519 discloses an agent comprising a prostaglandin I_2 derivative as an ammonium salt. The Examiner admits that JP '519 does not teach a specific ratio, specific ammonium compounds and specify PG I_2 compound, but states this could be determined by routine experimentation. In response, Applicants respectfully traverse the rejection.

> As set forth in M.P.E.P. § 2143, "[t]o establish a *prima facie* case of obviousness, *three* basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

All three elements set forth above must be present in order to establish a *prima facie* case of obviousness. Applicants assert that a *prima facie* case of obviousness has not been established for the following reasons: 1) there is no suggestion or motivation to modify the references; 2) there is no reasonable expectation of success; and 3) the cited art references do not teach or suggest all the claim limitations.

1. There is no Suggestion or Motivation to Modify the References

Applicants state that there is simply no motivation or suggestion provided in the cited references to modify their teaching in the way the Examiner has contemplated. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The invention disclosed in JP-'519 is directed to a second use of beraprost, that is, a therapeutic use of beraprost for nervous disorders caused by diabetes. As disclosed therein, an active ingredient ammonium salt of beraprost can be produced according to the method described in JP-A-58-1 24778, Paragraph 1, in the Example. However, this reference merely discloses this ammonium salt as a ***single component***.

JP-'519 does not teach or suggest a sustained-release pharmaceutical composition containing two components *i.e.*, 1) an ionic prostanoic acid derivative, and 2) an ionic compound having an opposite charge to that of the ionic prostanoic acid derivative and capable of enhancing the hydrophobic property of the ionic prostanoic acid derivative.

In stark contrast to the prior art, the present invention is directed to a sustained-release pharmaceutical composition containing an ionic prostanoic acid derivative, and an ionic compound having an opposite charge to that of the ionic

prostanoic acid derivative and capable of enhancing the hydrophobic property of the ionic prostanoic acid derivative.

As such, there is simply no motivation or suggestion provided in the cited reference to modify its teaching in the way the Examiner has contemplated. According, Applicants respectfully request that the Examiner withdraw the rejection.

2. There is No Reasonable Expectation of Success

In addition, there is no reasonable expectation of success that the modification that the Examiner contemplates will succeed. "Both the suggestion and the expectation of success must be found in the prior art, not the Applicants' disclosure." *In re Dow Chem. Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988).

Applicants assert that there is absolutely no teaching or suggestion in JP-'519 to modify the teaching therein to arrive at the presently claimed invention. Rather, the Examiner has used the Applicants' disclosure as a blueprint to pick and choose features from the prior art in an attempt to reconstruct the presently claimed invention.

There is no reasonable expectation that the modification that the Examiner contemplates will succeed. JP-'519 does not teach or suggest a sustained-release pharmaceutical composition containing an ionic prostanoic acid derivative, and an ionic compound having an opposite charge to that of the ionic prostanoic acid derivative and capable of enhancing the hydrophobic property of the ionic prostanoic acid derivative. Advantageously, the ionic compound is capable of enhancing the hydrophobic property of the ionic prostanoic acid derivative.

Thus, the Examiner has used hindsight reconstruction of the cited art in an attempt to piece together the present invention. Hindsight reconstruction is impermissible and therefore, Applicants respectively request that the Examiner withdraw the rejection.

3. The Cited Art References Do Not Teach All Limitations of the Claims

The prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Applicants assert that the prior art references do not teach or suggest all the limitations of the claims and therefore, the obviousness rejection in untenable.

Applicants claim a sustained-release pharmaceutical composition containing an ionic prostanoic acid derivative, and an ionic compound having an opposite charge to that of the ionic prostanoic acid derivative. Under *In re Wilson supra*, a *prima facie* case of obviousness has not been established because each of the limitation of the claims is not taught or suggested in the cited art references. Therefore, Applicants respectively request that the Examiner withdraw the rejection.

SECOND REJECTION UNDER 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-7 and 11-15 under 35 U.S.C. § 103(a) as allegedly being obvious over JP 04356422 ("JP '422"). The Examiner alleges that JP '422 teach a prostaglandin I_2 derivative plus sodium oleate, and further states that JP '422 does not teach the instant ratio, specific ammonium compounds and specific PG I_2 compounds. The Examiner states that the optimal ratio of ionic compound and PG I_2 compound could be determined through routine experimentation. In response, Applicants respectfully traverse the rejection.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

JP '422 teaches a fat emulsion formulation containing a specific prostaglandin I_2 derivative esterified with alkyl groups. As described therein, the object

of that invention is to provide a chemically stable and slow release type formulation. As is clear from the English Abstract, the formulation contains a specific prostaglandin I_2 derivative esterified with alkyl groups and sodium oleate. The prostaglandin I_2 derivative as taught therein, is ***not*** an ***ionic prostaglandin I_2*** derivative since it is esterified with ***nonionic*** alkyl groups.

Thus, JP-'422 does not teach or suggest the use of an ionic compound having an opposite charge to that of the ionic prostaglandin I_2 derivative and capable of enhancing the hydrophobic property of the ionic prostaglandin I_2 derivative in combination with an ionic prostaglandin I_2 derivative by any means.

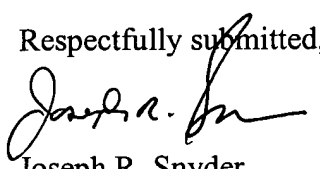
As such, the present invention is not obvious in view of JP-'422. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

CONCLUSION

In view of the foregoing remarks, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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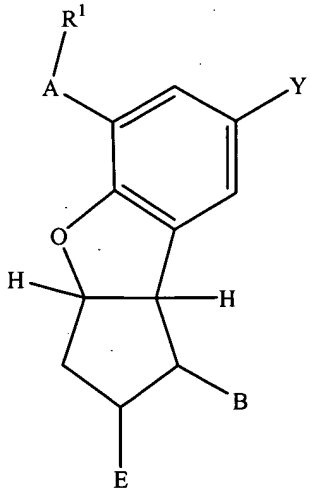
APPENDIX

1. A sustained-release pharmaceutical composition for an ionic prostanoic acid derivative comprising an prostanoic acid derivative and an ionic compound having an opposite charge to that of the ionic prostanoic acid derivative and increasing hydrophobicity of the prostanoic acid derivative.

2. A sustained-release pharmaceutical composition according to claim 1, wherein the ionic compound having an opposite charge to the ionic prostanoic acid derivative and increasing the hydrophobic property of the prostanoic acid derivative contains a hydrophobic group in the molecule thereof.

3. (Previously amended) A sustained-release pharmaceutical composition according to claim 1, wherein the ionic prostanoic acid derivative is a prostaglandin I_2 derivative.

4. (Previously amended) A sustained-release pharmaceutical composition according to claim 1, wherein the ionic prostaglandin I_2 derivative is a compound represented by the following general formula (I):



wherein R^1 represents $COOR^2$ (wherein R^2 represents:

1) hydrogen or a pharmacologically acceptable cation,

2) $-Z-Ar^1$, wherein Z is a valence bond or a straight or branched alkylene shown by C_tH_{2t} wherein t is an integer of 1 to 6, and Ar^1 is 2-pyridyl, 3-pyridyl or 4-pyridyl;

3) $-C_tH_{2t}COOR^3$, wherein C_tH_{2t} has the same significance as defined above, and R^3 is hydrogen or a pharmacologically acceptable cation;

or,

4) $-C_tH_{2t}N(R^4)_2$, wherein C_tH_{2t} has the same significance as defined above, and R^4 is hydrogen, a straight alkyl having 1 to 12 carbon atoms or a branched alkyl having 3 to 14 carbon atoms);

A represents:

1) $-(CH_2)_m-$, wherein m is an integer of 1 to 3;

2) $-CH=CH-CH_2$;

3) $-CH_2-CH=CH-$;

4) $-CH_2-O-CH_2-$;

5) $-CH=CH-$;

6) $-O-CH_2-$; or,

7) $C\equiv C-$;

Y represents hydrogen, an alkyl having 1 to 4 carbon atoms, chlorine, bromine, fluorine, formyl, methoxy or nitro;

B represents $-X-C(R^5)(R^6)OR^7$ (wherein R^5 represents hydrogen or an alkyl having 1 to 4 carbon atoms; R^7 represents hydrogen, an acyl having 1 to 14 carbon atoms, an aroyl having 6 to 15 carbon atoms, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl or t-butyl; X represents:

1) $-CH_2-CH_2-$;

2) $-CH=CH-$;or

3) $-C\equiv C-$;

R^6 represents:

1) a straight alkyl having 1 to 12 carbon atoms or a branched alkyl having 3 to 14 carbon atoms;

2) -Z-Ar^2 wherein Z has the same significance as defined above and Ar^2 is phenyl, α-naphthyl, β-naphthyl or a phenyl substituted with at least one of chlorine, bromine, fluorine, iodine, trifluoromethyl, an alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl or phenoxy;

3) -$C_tH_{2t}OR^8$, wherein C_tH_{2t} has the same significance as defined above, and R^8 is a straight alkyl having 1 to 6 carbon atoms, a branched alkyl having 3 to 6 carbon atoms, phenyl, a phenyl substituted with at least one of chlorine, bromine, fluorine, iodine, trifluoromethyl, an alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl or phenoxy, cyclopentyl, cyclohexyl, or a cyclopentyl or cyclohexyl substituted with 1 to 4 straight alkyl group(s) having 1 to 4 carbon atoms;

4) -Z-R^9, wherein Z has the same significance as defined above, and R^9 is hydrogen, a cycloalkyl having 3 to 12 carbon atoms or a substituted cycloalkyl having 3 to 12 carbon atom which is substituted with 1 to 3 alkyl groups having 1 to 5 carbon atoms;

5) -C_tH_{2t}-CH=C(R^{10})R^{11}, wherein C_tH_{2t} has the same significance as defined above, and R^{10} and R^{11} represent hydrogen, methyl, ethyl, propyl or butyl; or

6) -C_uH_{2u}-C≡C-R^{12}, wherein u is an integer of 1 to 7, C_uH_{2u} is a straight or branched alkylene and R^{12} is a straight alkyl having 1 to 6 carbon atoms);

E represents hydrogen or OR^{13}, wherein R^{13} is hydrogen, an acyl having 1 to 12 carbon atoms, an aroyl having 7 to 18 carbon atoms, a straight alkyl having 1 to 12 carbon atoms or a branched alkyl having 3 to 14 carbon atoms; or a salt thereof.

5. (Previously amended) A sustained-release pharmaceutical composition according to claim 1, wherein the ionic compound increases the oil/water partition coefficient of the ionic prostanoic acid derivative.

6. (Previously amended) A sustained-release pharmaceutical composition according to claim 1, wherein the ionic compound is incorporated at least in an equimolar amount based on the ionic prostanoic acid derivative in terms of a charge ratio.

7. (Previously amended) A sustained-release pharmaceutical composition according to claim 1, wherein the ionic prostanoic acid derivative is anionic.

8. A sustained-release pharmaceutical composition according to claim 7, wherein the ionic compound is a compound containing a group selected from an ammonium, pyridinium, phosphonium and sulfonium group in the molecule thereof, or a salt thereof.

9. A sustained-release pharmaceutical composition according to claim 8, wherein the ionic compound contains at least one member selected from the group consisting of an alkyldimethylbenzylammonium salt, an alkyltrimethylammonium salt, an alkylpyridinium salt, an alkylamine salt and an alkylphosphonium salt.

10. A sustained-release pharmaceutical composition according to claim 9, wherein the ionic compound is benzalkonium chloride.

11. (Previously amended) A sustained-release pharmaceutical composition according to claim 1, wherein the ionic prostanoic acid derivative is a synthetic ionic prostanoic acid derivative.

12. (Previously amended) A sustained-release pharmaceutical composition according to claim 1, wherein the prostaglandin I_2 derivative is (±)-(1R*-2R*, 3aS*, 8bS*)-2,3,3a,8b-tetrahydro-2-hydroxy-1-[(E)-(3D*)-3-hydroxy-4-methyl-1-octen-6-ynyl]-1H-cyclopenta[b]benzofuran-5-butanoic acid, or a salt thereof.

13. (Previously amended) A sustained-release pharmaceutical composition according to claim 1, wherein the ionic prostanoic acid derivative is cationic.

14. A sustained-release pharmaceutical composition according to claim 13, wherein the ionic compound is a compound containing a carboxyl, sulfate, sulfonate or phosphate group in the molecule thereof, or a salt thereof.

15. A sustained-release pharmaceutical composition according to claim 14, wherein the ionic compound is sodium lauryl sulfate and/or sodium oleate.

16. (Previously amended) A sustained-release pharmaceutical composition according to claim 13, wherein the ionic prostanoic acid derivative is a synthetic ionic prostanoic acid derivative.